REMARKS

Review and reconsideration on the merits are requested.

Formalities

Applicants appreciate the Examiner returning initialed Form PTO/SB/08.

They address the rejections as set forth below.

Claim Rejections - 35 U.S.C. § 112

Claims 34-36 are rejected under the above section, second paragraph, as being indefinite.

The Examiner refers to "a method as claimed in claim 12, which comprises administering three times a day", and states it is unclear what Applicant is claiming as the language "which comprises" implies that the method of claim 12 contains the three times per day administration which it does not. The Examiner finds the language "administering three times a day" to be unclear as to what is being administered or who it is being administered to.

Applicants amend claim 34 in a manner which, it is believed, responds to the rejection and request withdrawal.

However, if Applicants have misunderstood the Examiner's position, the Examiner is requested to contact the undersigned prior to issuing another Action on this point so that this issue may be resolved by a telephone interview.

Withdrawal is requested.

Claim Rejections - 35 U.S.C. § 103

Claims 12, 14, 24 and 34-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Clinical and Experimental Pharmacology Physiology, 2002, vol. 29, pp. 423-427, Ichikawa et al (Ichikawa).

This rejection is respectfully traversed.

The Examiner's position is set forth in the Action and will not be repeated here in detail except as necessary to an understanding of Applicants' traversal which is now presented.

Traversal

It seems that the Examiner's rejection is based upon a criticism of the DECLARATION...1.132 of Yuji Kiyono filed December 8, 2008, the Examiner finding the same not persuasive because the study cited in the DECLARATION used healthy volunteers, which would mean none of the patients studied fit the patients of the claims which require a type II human diabetic patient.

The Examiner further reasons that diabetic patients would clearly have a different response to sugar, have different postprandial blood sugar levels and reactions, and would also be expected to react to medication or treatments differently (than healthy patients).

Applicants believe that the Examiner is in error, and that the results obtained in healthy volunteers quite clearly demonstrate the significance of the administration timing of "within ten minutes before starting meal" for the reasons now set forth.

The insulin secretion response in diabetic patients can vary. In fact, *insulin secretion after meal* (responding to sugar) in diabetic patients is delayed in comparison with normal subjects, depending upon the severity of the diabetes. See Mebio, Extra issue, 2003, submitted with the Information Disclosure Statement considered 02/15/2008, partial translation.

However, mitiglinide calcium hydrate, the compound of the method claims herein, is an insulin secretion enhancer, and it has been confirmed that the *insulin secretion by administration of the drug occurs in a similar fashion in diabetic animals and normal animals.* Applicants explain this matter by submitting herewith Ojima et al, Folio Pharmacol. Jpn., Vol. 124, 2004, pp. 245-255, hereafter referred to as Ojima.

Referring to Ojima, Fig.6 (A) shows plasma insulin levels (ng/mL) after administration of mitiglinide calcium hydrate (hereinafter referred to as "mitiglinide") in normal rats after a sucrose load. Since the control group was not administered mitiglinide, the insulin secretion in the control group (O) was caused only by sucrose. Therefore, the difference between the mitiglinide group and the control group can be considered as insulin secretion due to mitiglinide itself. It can be seen that the insulin secretion by 1mg/kg (▲) of mitiglinide administration reached its peak at 15 min after administration in normal rats.

In Ojima, Fig. 9 (B) shows plasma insulin levels (ng/mL) after administration of mitiglinide in diabetic rats after a sucrose load. From the graph of the control group, delayed insulin secretion caused by sucrose was seen in comparison with the control group in normal rats (the above mentioned Fig.6 (A)). However, the difference between the insulin levels in the mitiglinide 1mg/kg group (●) and the control group (O) reached its peak at around 15 to 30 min after administration, even in diabetic rats. Thus, these results demonstrates that the insulin secretion responses to administration of mitiglinide are almost the same in normal rats and diabetic rats.

Accordingly, the timing of the insulin secretion in diabetic patients after the administration of mitiglinide calcium hydrate can be expected to be almost the same as that in healthy volunteers. That is, as seen in healthy volunteers, there would be a higher risk that a decrease in blood glucose level before meal occurs when the drug is administered at 30 min before meal than within 10 min before meal, because of insulin secretion before meal. Therefore, Applicants believe that the administration timing in the present invention is critical based on the results shown in the submitted DECLARATION…1.132.

Applicants attach hereto for the Examiner's consideration Figures A and B. Figures A and B are basically modified Fig. 6 (A) and Fig. 9 (B) respectively of Ojima.

Figure A shows the plasma insulin levels in control groups in normal rats (control group of Fig.6(A)) and diabetic rats (control group of Fig.9(B)). It can be seen that the insulin secretion in diabetic rats **after meal** is delayed in comparison with normal rats. In contrast, Figure B shows the difference in plasma insulin level between Mitiglinide 1 mg/kg group and the corresponding control group each in normal rats (calculated from the data of Fig. 6(A)) and diabetic rats (calculated from the date of Fig. 9(B)). It can be seen that the insulin secretion **caused by the administration of mitiglinide** in diabetic rats occurs in a similar manner as compared with normal rats.

The Issue of Doses in Ichikawa

In the Action at page 5, the Examiner states (paraphrased):

"[Ichikawa] also teaches dosages of 0.3-1 mg/kg (page 424, Table 1).

***

The dosage of 0.3-3 mg/kg, in a 120 lb. (55 kg) patient would be a range of 16-165 mg. While 16 mg is still larger than 10-11 mg claimed, some routine optimization is well within the skills of one of ordinary skill in the art and in translating dosages from rats to humans, one would expect some variation and need to optimize. Furthermore, there is a motivation to use as small a dosage as possible that is effective in humans to decrease the side effects."

Applicants respectfully submit that dose of the present invention (10 to 11 mg) is unobvious to one of ordinary skill in the art from the teaching in Ichikawa. Although Ichikawa used doses in a range of 0.3, 1 and 3 mg/kg of KAD-1229 in the studies, the lowest dose of 0.3 mg/kg (16.5 mg per 55 kg patient) is not effective in diabetic rats (Table 1, Fig. 1(a), Fig. 2(a)). The effective dose is 1 mg/kg (55 mg per 55 kg patient) or more, which is very high. Therefore, one of ordinary skill in the art would not expect a low dose of 10 to 11 mg would be useful for the method of the present invention.

In addition, although the Examiner cites some portions from MPEP 2144.05 which states that it is not inventive to discover optimum or workable ranges by routine experimentation, in the field of pharmaceuticals, one of ordinary skill in the art would generally determine dosages by conducting designed clinical studies based on accumulated knowledge including the results obtained in animal experiments.

As a consequence, Applicants respectfully submit that it would not be obvious to one of ordinary skill in the art to reach the specific dose of 10 to 11 mg of the present invention based on the teaching in Ichikawa that 16.5 mg is not effective and 55 mg or more is effective.

Applicants thus respectfully submit that based on the teaching in Ichikawa, optimization is not involved, rather, one of ordinary skill in the art from the teaching of Ichikawa would find Ichikawa to contain a **teaching against** the present invention.

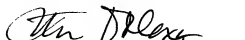
In summary, the present invention was reached based on the unexpected results obtained by the present method based on specific administration timing and specific dosage. According to the administration method of the present invention, mitiglinide calcium salt hydrate exerted unexpectedly superior effects such as lowering postprandial hyperglycemia and fasting glucose level without causing prolonged hypoglycemia in comparison with voglibose, a widely-used antidiabetic agent, and therefore, it is submitted that the present invention is unobvious from Ichikawa.

Withdrawal of all rejections and allowance is requested.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Peter D. Olexy
Registration No. 24,513

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860
WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: August 31, 2009